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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/039,645	10/25/2001	Alan S. Kopin	00398/510002	9279

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EXAMINER	
BERTOGLIO, VALARIE E	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 01/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

S.M.

Office Action Summary	Application No.	Applicant(s)	
	10/039,645	KOPIN ET AL.	
	Examiner	Art Unit	
	Valarie Bertoglio	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *20 October 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05/01/2002* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *06/20/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's amendment filed on 10/20/2003 has been entered. Claim 3 has been amended. Claims 1-33 are pending and under consideration in the instant action.

Claim Rejections - 35 USC § 112-1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-33 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The rejection is maintained for reasons of record set forth on pages 2-6 of the office action mailed 04/17/2003.

Claims are directed to using gene therapy to treat, reduce or prevent pain wherein the gene is a constitutively active and hypersensitive mu opioid receptor gene. The specification teaches that single Asn to Ala point mutation at amino acid 150 of SEQ ID NO:1 renders the rat mu opioid receptor constitutively active and hypersensitive *in vitro*, i.e. it is active in the absence of an agonist and has a higher affinity for agonists. The rejection is on the grounds that *in vitro* function of an expression vector does not provide a prediction of therapy for any pain condition as the results only pertain to constitutive activation of the mu opioid receptor in HEK293 cells in vitro.

Applicant argues that case law does not support a requirement of in vivo experimental data. Applicant argues "[The] specification need not contain an example if the invention is

otherwise disclosed in such a manner that one skilled in the art will be able to practice it without undue experimentation. In re Borkowski, 422 F.2d 904, 908, 164USPQ 642, 645 (CCPA 1970)" (applicant's response page 10, lines 7-11). This argument is not persuasive because the specification fails to disclose the invention in such a manner that one skilled in the art will be able to practice it without undue experimentation. The specification does not teach how to administer the claimed gene to an individual or the dosage required to result in the treatment of pain. The specification teaches the in vitro activity of a gene that has the potential to treat pain but the specification does not teach how to use the vector in vivo to overcome the unpredictability and underdeveloped nature and understanding of in vivo gene therapy. The specification fails to provide a correlation to therapeutic levels of expression of a nucleic acid in an in vivo setting in any subject having pain.

In response to Applicants' arguments, as set forth in the previous office action, the state of the art of in vivo gene therapy is highly unpredictable and there are a number of variables and parameters involved in treating an individual using gene therapy that must be defined for any method of therapy to be effective (refer to pages 3-5 of the previous office action). These parameters include the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate (refer to Eck and Wilson, 1996, "Gene-Based Therapy" in The Pharmacological Basis of Therapeutics, pages 81-82)

All of these parameters can variably affect the efficacy of a mode of gene therapy treatment. With specific respect to treating pain using gene therapy, Iadarola taught that the efficacy depends on many factors, mainly the vector and route of administration (1997, *Molecular Neurobiology of Pain*, Vol. 9, page 353-354, Discussion 1st and 2nd paragraphs). Iadarola taught that the promoter used to drive expression of the target gene can vary the level and duration of expression (page 355, 1st full paragraph) and concludes that while several potential routes of gene therapy administration exist, each has its own set of advantages and constraints (page 356, last paragraph).

The instant specification does not provide any working examples correlating to the treatment of pain. The specification has only provided prophetic discussions as to how one might treat pain using a nucleic acid encoding constitutively active or hypersensitive mu opioid receptor. The specification does not provide the guidance necessary to overcome the unpredictability and uncertainty of gene therapy set forth in the art. For example, the specification does not teach which DNA vectors will effectively transduce cells to treat pain. The specification does not teach which cell types should be transfected to treat pain. The specification provides a list of potential vectors (for example see page 3, lines 18-19; page 45, line 5- page 50, line 1) as well as a list of potential routes of administration (page 51, line 11- page 52, line 9) that are not specific to any gene therapy treatment regimen and does not teach which vector or route of adminstration will work effectively to treat pain using the constitutively active or hypersensitive mu-opioid receptor gene.

According to Eck and Wilson, it is important to tailor a gene therapy vector and methods to specific diseases and disorders (see page 82, column 1, 1st paragraph). The specification offers

no guidance as to how to tailor the constitutive and hypersensitive mu-opioid receptor gene to effectively treat pain. For example, the specification does not teach which types of vector will result in the desired levels of infection of particular tissues resulting in the proper levels of gene expression for therapy. The specification does not even define what levels of expression or what tissues should express the gene for a therapeutic effect.

Applicant further argues that a number of studies using gene therapy in animal models had been performed successfully. While it is agreed that gene therapy has been shown effective to treat some disease states, it is maintained that the variables involved (the type of vector, mode of delivery, etc.) are specific to each disease and gene. The specification fails to be enabling because it does not provide the guidance necessary to determine how to use the claimed mu-opioid receptor gene to treat pain in vivo. The success of other treatment regimens has no relevance to the lack of guidance in the instant specification as the specification fails to provide any correlation between the parameters used for successful treatment of specific diseases using specific vectors and routes of administration as set forth in the art and the parameters that are necessary to treat pain using the mu-opioid receptor gene of the instant invention. Therefore, in light of the lack of guidance in the specification with respect to how to use the constitutive and hypersensitive mu-opioid receptor gene to treat pain in vivo, the enablement rejection is maintained.

Claim 3 has been amended to read on a single point mutation of Asn to Ala at amino acid 150 of SEQ ID NO:78. However, an Asn residue is not present at amino acid 150. Amino acid 150 is Tyr. The specification does not teach how to mutate the Asn residue of amino acid 150 of SEQ ID NO:78 because this residue does not exist.

Applicant's arguments with respect to the adverse effects of the claimed invention are persuasive and this aspect of the rejection is withdrawn.

Claim Rejections - 35 USC § 112-2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

In light of Applicant's arguments and amendment to claim 3, the rejection of claims 1-33 under 35 USC 112, 2nd paragraph is withdrawn.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is 703-305-5469. The examiner can normally be reached on Mon-Fri 6:00-2:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on 703-305-4051. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1234.

Note: After January 13, 2004, the Examiner may be reached at (571) 272-0725, and should the Examiner be unavailable, inquiries may be directed to Deborah Reynolds, SPE of Art Unit 1632 at (571) 272-0734.

PETER PARAS
PATENT EXAMINER

Valarie Bertoglio
Patent Examiner